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DATA EVALUATION RECORD

STUDY 2

CHEM 109801 **Iprodione** §161-2

FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 41861901
Adrian, P.P. and J. Robles. 1991. *^{14}C-Iprodione Aqueous Photolysis.* Laboratory Project ID: Study No. 90-22. Filing Reference: AG/CRLD/AN/9115524. Unpublished study performed by Rhône-Poulenc Secteur Agro, Lyon, France, and submitted by Rhône-Poulenc Ag Company, Research Triangle Park, NC.

DIRECT REVIEW TIME = 8

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DATE: December 2, 1991.

CONCLUSIONS:

Degradation - Photodegradation in Water:

1. The submitted study is unacceptable and cannot be used to fulfill the Photodegradation in Water (161-2) data requirement at this time.

2. The data are considered to be of uncertain value and should not be used to predict the environmental behavior of iprodione.

3. This study is unacceptable at this time for the following reasons:

Sufficient information was not provided to adequately assess the photodegradation of iprodione; sampling intervals for irradiated and dark control test solutions were reported in terms of days of equivalent Florida summer sunlight rather than the actual post-treatment sampling intervals, and a measured total irradiant intensity of the artificial light source was not reported.

There are significant discrepancies in the formation of [^{14}C]volatiles between the reaction vessels that were only periodically flushed with air versus continuous air-flow.

The description of the methodology was vague and incomplete.

4. In order for this study to be reconsidered for review, the registrant must provide the actual post-treatment sampling intervals, report the measured total irradiant intensity of the artificial light source with a comparison to natural sunlight, address the discrepancies in the production of [^{14}C]volatiles between the intermittent versus continuous air-flow systems, and adequately describe the test methodology.

METHODOLOGY:

Phenyl ring-labeled [^{14}C]iprodione (uniformly labeled, radiochemical purity >99%, specific activity 739.8 MBq/mMol, Commissariat à l'Energie Atomique) plus unlabeled iprodione (purity 99.9%, Rhône-Poulenc Agro), dissolved in acetonitrile, was added at a nominal concentration of 5 ppm to a sterile aqueous 0.02 M citric acid-buffered solution (pH 5) contained in a Pyrex glass reaction vessel; the final concentration of the co-solvent (acetonitrile) was 1%. Reaction vessels (unspecified number) were prepared and sealed with screw-cap lids equipped with optical silica glass windows (Figure 5). The reaction vessels were placed in a photolysis apparatus (Heraeus Suntest) and irradiated continuously using a xenon arc lamp equipped with a UV filter to eliminate radiation below 290 nm (Figure 7). The test solutions were magnetically stirred during irradiation and maintained at 25 ± 1 °C using a refrigerated circulating water bath. Four additional reaction vessels were prepared, wrapped in aluminum foil, and incubated in the photolysis apparatus to serve as dark controls. Duplicate irradiated reaction vessels were removed for analysis at 0, 4, 8.6, 15.3, 16.9, and 32.9 days of irradiation equivalent to Florida summer sunlight. Dark control vessels were removed for analysis at the 16.9- and 32.9-day sampling intervals for the irradiated solutions. At each sampling interval, sterile, humidified CO_2-free air was drawn through each reaction vessel (air flow rate unspecified), then sequentially through tubes containing ethylene glycol monomethylether (one tube), 2 N sodium hydroxide (two tubes), and 2 N sulfuric acid (one tube) trapping solutions, and through a XAD-4 resin (one tube).

Samples were partitioned twice with methylene chloride and once with ethyl acetate. The methylene chloride phases were combined and aliquots of the methylene chloride phase, ethyl acetate phase, and the remaining aqueous

phase were analyzed for total radioactivity using LSC. The organic phases were concentrated (method not reported) and analyzed using one-dimensional TLC on silica gel plates developed in toluene:ethyl acetate (80:20, v:v; Solvent System 1) or methylene chloride:ethyl acetate:formic acid (90:7.5:2.5, v:v:v; Solvent System 2). Radioactive areas were detected and quantified using a TLC radioanalyzer; autoradiography was also used for visualization. Methylene chloride phases were also analyzed using reverse-phase HPLC on a C-18 deactivated C-8 column eluted with 10% acetonitrile in pH 5 phosphate buffer:acetonitrile (55:45, v:v) with flow-through UV (210 nm) and radioactivity detection. When >10% of the applied radioactivity was detected in the aqueous phase, the aqueous phase was acidified to pH 1.5 (method not reported) and repartitioned twice with ethyl acetate. The ethyl acetate phases were combined and aliquots were analyzed using TLC developed in Solvent Systems 1 and 2, plus butanol:acetic acid:water (85:15:5, v:v:v; Solvent System 3) and chloroform:methanol:formic acid:water (75:20:4:2, v:v:v:v; Solvent System 4). The remaining aqueous phase was concentrated to dryness under vacuum, the residues were redissolved in water:methanol (90:10, v:v), and the solution was applied to a Sephadex LH-20 column eluted with water:methanol. The eluate was concentrated (method not reported), and aliquots were analyzed using TLC developed with Solvent Systems 3 and 4. Degradate identifications were confirmed using HPLC/MS with electron impact and negative chemical ionization.

Trapping solutions were analyzed for total radioactivity using LSC. The presence of CO_2 in the sodium hydroxide trapping solutions was confirmed using barium chloride precipitation. The XAD-4 resin was extracted with ethyl acetate using sonication, then analyzed by LSC.

To further investigate the production of volatiles, additional reaction vessels containing [^{14}C]iprodione-treated buffer solution were prepared, attached to the gas collection system, and irradiated as described above. In this portion of the experiment, however, air was continuously passed (rate unspecified) through the reaction vessels, then through the trapping solutions and solid phase resin. The traps were changed after 6.68, 15.03, and 33.35 days of equivalent Florida summer sunlight; the trapping solutions and XAD-4 resin were analyzed as described above.

In a separate experiment, reaction vessels (unspecified number) containing [^{14}C]iprodione-treated buffer solution were prepared as described above and the test solutions were sensitized with 2% acetone (by volume). Two of the reaction vessels were irradiated as described above and one was maintained as a dark control; the vessels were attached to a gas collection system with continuous air flow (rate unspecified). At unspecified sampling intervals, an aliquot (100 μL) was removed from each reaction vessel and analyzed for iprodione using reverse-phase HPLC. At the final sampling interval, the test solutions were extracted with methylene chloride and the extracts were analyzed using reverse-phase HPLC and HPLC/MS as previously described.

DATA SUMMARY:

Phenyl ring-labeled [^{14}C]iprodione (uniformly labeled, radiochemical purity >99%), at a nominal concentration of 5 ppm, photodegraded with a registrant-calculated half-life of 67 days in sterile aqueous citric acid-buffered solutions (pH 5) that were irradiated continuously with a UV-filtered xenon arc lamp at 25 °C for 33 days of equivalent Florida summer sunlight. In contrast, [^{14}C]iprodione did not significantly degrade in a similar solution incubated in the dark; at the 16.9- and 32.9-day sampling intervals for the control samples, iprodione comprised an average of 90.6% and 97.8% of the applied, respectively (Table VI). The major degradate in both the irradiated and dark control non-sensitized solutions was 1-(3,5-dichlorophenyl)carbamoyl-3-isopropylhydantoin (RP-30228).

In the irradiated non-sensitized solutions after 33 days of equivalent Florida summer sunlight, iprodione comprised an average of 67.8% of the applied radioactivity, RP-30228 comprised an average of 1.9% (maximum 2.73% at 16.9 days), and 1-isopropylcarbamoyl-3-(3,4-dichlorophenyl)hydantoin (RP-40837) comprised an average of 1.3% (maximum 2.75% at 4 days). Unidentified organosoluble radioactivity comprised ≤5.89% of the applied during the study. Polar extractables (pH 1.5 ethyl acetate extracts) and aqueous-soluble [^{14}C]compounds comprised a maximum of 10.42 and 17.09% of the applied radioactivity, respectively, after 15.3 days of equivalent Florida summer sunlight; analysis of the extracts and organic phases detected [^{14}C]compounds each comprising an average of ≤7.2% of the applied (Table IV). In irradiated non-sensitized solutions where volatiles were flushed from the reaction vessels only at each sampling interval, [^{14}C]volatiles totalled an average of 0.7% of the applied after 33 days of equivalent Florida summer sunlight (Table IV). However, when exposed to a continuous air-flow system, volatilization (primarily $^{14}CO_2$) from the irradiated non-sensitized solutions totaled an average of 23.5% after 33 days of equivalent Florida summer sunlight (Table V); these test solutions were not analyzed for parent iprodione. During the study, material balances ranged from 87.99% to 102.89% of the applied (Tables IV and V).

Uniformly phenyl ring-labeled [^{14}C]iprodione, at a nominal concentration of 5 ppm, photodegraded with a registrant-calculated half-life of 22 days (r^2 = 0.74) in irradiated, sensitized (2% acetone), sterile, aqueous citric acid-buffered solutions (pH 5); quantitative data were not provided (Figure 36). In the irradiated sensitized solutions, the primary degradate was RP-40837. Other degradates identified included carbamoyl-1-(3,5-dichlorophenyl)-3-hydantoin (RP-32490), isopropylcarbamoyl-1-(3,5-dichloro-4-hydroxyphenyl)-3-hydantoin (RP-37677), 1-isopropylcarbamoyl-3-(3-chlorophenyl)hydantoin (RP-25331), and two isomers of iprodione.

COMMENTS:

1. The actual intervals that irradiated and dark control samples were removed from the photolysis apparatus were not reported. The study authors reported sampling intervals in days equivalent to Florida summer sunlight. Numerous equations were provided to show how the intensity of the xenon arc lamp was converted to days of equivalent Florida summer sunlight, but actual calculations were not reported.

2. A spectral distribution of the xenon arc lamp was provided; however, a measured total irradiant intensity of the light source was not reported. It was reported that the radiant intensity of the light source at the height of the reaction vessel was measured at each sampling interval using a radiometer, but that information was not provided.

3. There is a significant discrepancy in the production of [^{14}C]volatiles between the test solutions that had air drawn through the reaction vessels only at each sampling interval, and the test solutions that had air drawn through the vessels continuously. After approximately 33 days of equivalent Florida summer sunlight, [^{14}C]volatiles totaled 0.58-0.77% of the applied radioactivity in the test solution with intermittent volatile collection and 22.8-24.1% of the applied (primarily $^{14}CO_2$) in the test solution with continuous air-flow. Material balances were essentially equivalent for the test solutions; 92.7-93.4% of the applied for the test solution with intermittent volatile collection and 93.9-94.1% for the test solution with continuous air-flow. The test solution with continuous air-flow was not analyzed for parent iprodione and its degradates, and a dark control was not conducted for this separate experiment. The study authors did not attempt to explain the discrepancy.

4.

4. It was reported in the Experimental section (specifically section 2.10) of the study write-up that the non-sensitized test solutions were irradiated in duplicate; however, it could not be determined if three photolysis reaction vessels were prepared for irradiation (including one dark control) and aliquots were collected from these vessels at each sampling interval, or if fourteen vessels were prepared for irradiation (including four dark controls) and two vessels were collected at each interval. The wording of the study write-up implied that duplicate irradiated vessels were prepared for each sampling interval. If, however, only three reaction vessels were prepared (two irradiated and one dark control), the volume of the aliquot removed from the reaction vessels at each sampling interval must be reported.

Likewise, in the sensitized test solutions experiment, the number of reaction vessels was indeterminable.

5. Apparently degradate identifications were made by comparison to unlabeled reference standards, but for the TLC analyses it was not specified if the reference standards were co-chromatographed with the samples, or if identifications were made by comparison to predetermined R_f values; it was also not reported how unlabeled reference standards were visualized. For the HPLC analyses, it was not reported if unlabeled reference standards were run with each set of samples.

6. The absorption spectrum of iprodione in the test solution was not provided.

7. For the experiment using sensitized (2% acetone) test solution, the sampling intervals were not specified; however, according to Figure 36, the intervals were reviewer-estimated to be 3, 7, 10.5, and 24 days of irradiation equivalent to Florida summer sunlight. In addition, quantitative data to support the calculated half-life were not provided. Figure 36 indicated, as did the half-life linear regression correlation coefficient ($r^2 = 0.74$), that the data were highly variable.

8. In the results for the sensitized irradiated solution, one of the degradates was listed as RP-42290. However, it was not identified in the degradation pathways nor was it identified as a reference standard. The degradate carbamoyl-1-(3,5-dichlorophenyl)-3-hydantoin (RP-32490) was identified in the degradation pathways and reference standards list. The Dynamac reviewer considered the use of RP-42290 to be a typographical error and used RP-32490 in this review.